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## CHAPTER 10

### Determining the incidence of Pneumocystis Pneumonia in patients with autoimmune blistering diseases not receiving routine prophylaxis

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## Abstract

**Importance** Pneumocystis pneumonia (PCP) is a potentially lethal opportunistic infection that primary prophylaxis can help prevent. The risk of prophylactic therapy must be weighed against the incidence of PCP in the patient population. Prophylaxis most frequently involves trimethoprim-sulfamethoxazole, with second-line therapies, including atovaquone, dapsone, and pentamide. The indication for prophylaxis in immunocompromised patients without HIV is less well defined. Previously, an incidence of at least 3.5% has been proposed as a cutoff to justify prophylaxis.

**Objective** To assess the incidence of PCP in patients with autoimmune blistering diseases receiving no routine prophylaxis.

**Design, setting, and participants** This was a retrospective analysis of patient medical records to determine the incidence of PCP infections. The multicenter study was performed at tertiary care centers that provide care for patients with autoimmune blistering diseases in Germany, Italy, Singapore, Israel, and the Netherlands. Patients had a confirmed diagnosis of pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, epidermolysis bullosa acquisita, mucous membrane pemphigoid, or anti-p200 pemphigoid.

**Main outcomes and measures** To determine the incidence of PCP defined as patients with the International Classification of Diseases, Ninth Revision (ICD-9), code 136.3, for PCP, or free text documentation of PCP occurring based on characteristic radiographic findings with elevated lactate dehydrogenase, or hospitalization for pneumonia with bronchioalveolar lavage demonstrating *Pneumocystis jiroveci* on confirmatory stains.

**Results** A total of 801 patients with autoimmune blistering diseases were included in this study; their mean (SD) age was 66.5 (17.6) years, and a total of 465 (58%) were female. Only 1 patient developed PCP, resulting in an incidence rate of 0.1%. This incidence significantly fell below the recommended threshold of 3.5% (0.1% vs. 3.5%,  $\chi^2_1 = 27.0$ ;  $P < .001$ ). This incidence was significantly lower than the previously reported incidence of PCP in all immunosuppressed dermatologic patients (0.1% vs. 1.3%;  $\chi^2_1 = 8.2$ ;  $P = .004$ ).

**Conclusions and relevance** Routine PCP prophylaxis for patients with autoimmune blistering diseases does not seem to be warranted. Patients with autoimmune blistering diseases seem to have a lower risk of PCP than the general population of immunosuppressed dermatology patients. Risks of routine prophylaxis include hyperkalemia, hypoglycemia, photosensitivity, thrombocytopenia, and more rare adverse reactions.

## Introduction

Pneumocystis pneumonia (PCP) is an opportunistic fungal infection caused by *Pneumocystis jiroveci*, formerly named *Pneumocystis carinii*.<sup>1</sup> PCP can occur in the setting of human immunodeficiency virus (HIV), as well as in the setting of congenital or iatrogenic immunosuppression. Its incidence in patients with HIV has been significantly decreased with the use of routine prophylaxis in patients with CD4+ T lymphocyte counts of less than 2000. Prophylaxis most frequently involves trimethoprim sulfamethoxazole, with second-line therapies, including atovaquone, dapsone, and pentamide. The indication for prophylaxis in immunocompromised patients without HIV is less well defined.

Meta-analysis of immunocompromised patients with HIV has suggested a PCP incidence of at least 3.5% to outweigh the risks of therapy.<sup>2</sup> These risks include hyperkalemia, hypoglycemia, photosensitivity, thrombocytopenia, and more rare adverse reactions, such as Stevens-Johnson syndrome, agranulocytosis, aplastic anemia, drug reaction with eosinophilia and systemic symptoms, and fulminant hepatic necrosis. Other Cochrane meta-analyses of prophylactic trimethoprim sulfamethoxazole in immunocompromised patients without HIV demonstrated that adverse events necessitating the cessation of prophylaxis occurred in 13.8% of patients compared with 5.9% in patients receiving either placebo or alternative prophylactic antibiotics.<sup>3-5</sup> This results in a number needed to harm of 12.7, although this does not specify severe adverse events vs. minor adverse events.<sup>3</sup> While primary PCP prophylaxis with trimethoprim-sulfamethoxazole was found to improve survival in these patients, it is notable that the incidence of PCP in this cohort was estimated at 6.2%.<sup>4</sup> This patient population included afebrile neutropenic patients, children with leukemia, and both solid and bone marrow transplant patients, but notably did not include studies of patients with dermatologic diseases.

The use of prophylactic treatment in the iatrogenically immunosuppressed patient is controversial. Some have suggested use of primary prophylaxis for PCP for patients receiving and equivalent of at least 20 mg of prednisone daily for more than 4 weeks, particularly if a second risk factor exists, including malignant neoplasm, interstitial lung disease, or additional immunosuppressive therapies.<sup>6,7</sup> The disease in question, however, plays a significant role in the decision for PCP prophylaxis. Few studies have assessed the incidence of PCP in dermatologic patients. Lehman and Kalaaji<sup>8</sup> assessed 150 dermatology patients receiving

immunosuppressive therapy for more than a month, finding that PCP occurred in 0.5% of patients. A larger study of 334 patients with immunobullous and connective tissue disease receiving immunosuppressive therapies showed that 7 patients (2%) developed PCP, with a 1-month mortality rate of 43% in those patients.<sup>9</sup> Of the patients developing PCP, only 1 had an immunobullous disease. A Chinese study<sup>10</sup> of 202 patients with immunobullous disease demonstrated an incidence of PCP in 1.9%. In contrast, an Israeli study<sup>11</sup> of 172 patients following individuals newly diagnosed as having pemphigus failed to demonstrate any patients with PCP. Based on these studies, the incidence of PCP in the dermatologic immunosuppressed population can be estimated at 1.3%.<sup>3</sup> PCP carries a significant mortality in these patients, estimated at 47%.<sup>12</sup>

Patients with certain diseases carry a greater innate risk for PCP. For example, granulomatosis with polyangiitis (formerly Wegener granulomatosis) is associated with a PCP incidence of 6%. Therefore, it would be indicated to use primary PCP prophylaxis in these patients.<sup>13</sup> Thus, evidence-based guidelines must be based on the disease in question rather than a generalized immunosuppressed state.

Autoimmune blistering diseases (AIBDs) are characterized by circulating autoantibodies targeting epidermal antigens located at the basement membrane zone or in the epidermis, but sparing of the vasculature and other organs as would be involved in connective tissue disease. Patients with AIBD often require prolonged use of often multiple immunosuppressive therapies, putting them at risk for opportunistic infections.<sup>11</sup> Among experts in the treatment of immune bullous disease, there is significant discord in regard to use of opportunistic infection prophylaxis.<sup>14</sup> As such, we sought to characterize the incidence of PCP in a large cohort of patients with AIBD to generate evidence-based recommendations regarding routine PCP prophylaxis in these patients. We hypothesized that patients with AIBDs not receiving routine prophylaxis fail to reach a PCP incidence of 3.5% and that the current estimation of 1.3% in all dermatologic patients overestimates the incidence of PCP in patients with AIBDs.

## Methods

### Study design

A retrospective multicenter study was performed in 6 tertiary referral centers for AIBD. Study populations included Israel, Germany, the Netherlands, Italy, and Singapore. Routine use of PCP prophylaxis was not used at these institutions.

Following appropriate ethical approval for medical record review, medical records and/or databases were reviewed within each institution.

### **Inclusion and exclusion criteria**

Enrollment time was dependent on the availability of accurate medical records (ie, searchable electronic health records) or patient databases at each individual institution. Patients with a confirmed diagnosis of pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, epidermolysis bullosa acquisita, mucous membrane pemphigoid, or anti-p200 pemphigoid were included in the study. Diagnosis was based on each individual institutions' protocol for diagnosing AIBDs, which at a minimum required clinical suspicion and immunofluorescence studies confirming the disease in question, with most patients having histologic and additional serologic confirmation of disease subtype. Patients without a confirmed disease subtype or paraneoplastic pemphigus were excluded. In addition, patients who had received dapsone at any point during their treatment course, had received primary PCP prophylaxis, or had less than 3 months of follow-up available were excluded. All patients, regardless of whether they received systemic therapies, were included to minimize selection bias of more severe presentations, and to account for patients receiving variable doses of topical steroids, which may have systemic immunosuppressive effects. The cohort in the study by Leshem et al<sup>11</sup> as well as their method for data extraction has been described previously.

### **Power analysis**

Sample size was calculated to be greater than 429 to ensure an ability to detect an incidence of 1.3%, the reported incidence of PCP in dermatologic patients, compared with the proposed 3.5%, with an  $\alpha$  error of 0.05 and power of 80%. A secondary goal of a sample greater than 718 to determine whether the incidence of PCP in patients with AIBDs was significantly lower than in all immunosuppressed dermatologic patients, with an  $\alpha$  error of 0.05 and power of 80%. The enrollment period at each institution is detailed in table 1.

### **End points**

Enrollment was considered at the time of the first note written in the patient's medical record in the immunobullous disease clinic. Thus, outside referrals for poorly controlled disease or new diagnoses were treated the same, and both were

considered the starting time for enrollment. Follow-up was defined as the time from the first encounter within the clinic, up to the most recent note in the medical record and/or encounter or death, if recorded. In the case of patients receiving trimethoprim-sulfamethoxazole for non-PCP infections, follow-up was stopped at this point.

**Table 1.** A summary of participating institutions' enrollment

Institution	Enrolment years
Singapore General Hospital, Singapore	2005-2014
University of Genoa, Italy	2001-2016
Rabin Medical Center, Israel	2003-2012
Istituto Dermopatico dell'immacolata, Italy	1985-2016
University Medical Center Groningen, the Netherlands	2002-2016
Philipps University, Germany	2004-2016

Patient demographics were extracted, including age, sex, immunobullous disease subtype, systemic medications used for treating the immunobullous disease, associated chronic comorbidities, follow-up time, and the occurrence of PCP. Information on race or ethnicity was not routinely available. Comorbidities evaluated included diabetes, psoriasis, malignant neoplasm, and autoimmune diseases, with hypertension and osteoporosis serving as nonimmunosuppressive comorbidity controls. These were defined as either International Classification of Diseases, Ninth Revision (ICD-9), codes or free text recorded chronic comorbidities. The incidence of PCP was defined as patients with the ICD-9 code 136.3 for *Pneumocystis pneumonia* or free text documentation of PCP occurring based on characteristic radiographic findings with elevated lactate dehydrogenase or hospitalization for pneumonia with bronchioalveolar lavage demonstrating *Pneumocystis jiroveci* on confirmatory stains.

### Statistical analysis

Demographic characteristics were summarized descriptively. To determine the incidence of comorbidities, only cases with available information regarding comorbidities were taken into account. Thus, the incidence of each comorbidity was reported as incidence of cases in which comorbidities were available.  $\chi^2$  Tests



were used to compare the incidence of PCP in the study group compared with the proposed cut-off of 3.5% used to justify prophylaxis, as well as 1.3%, which was the mean incidence of PCP in dermatologic patients from the previously discussed literature review. Pertinent subgroup analysis of patients with PCP were additionally performed using a  $\chi^2$  test to compare subgroup incidence with the proposed 3.5% cut-off. All tests were 2-tailed and performed using the IBM SPSS statistical software, version 20.  $P < .05$  was considered statistically significant.

## Results

In total, 801 patients met the inclusion and exclusion criteria; their mean age (SD) was 66.47 (17.62) years, and a total of 465 (58%) were women. The mean follow-up time was 2.94 years, resulting in 2354 patient-years. Reasons for exclusion included use of dapsone (258 patients), insufficient follow-up (187 patients), and PCP prophylaxis given (6 patients). Additional demographic information is provided in table 2. Of these 801 patients, 1 developed PCP. This patient, a man in his 40s with recalcitrant mucocutaneous pemphigus vulgaris and no reported comorbidities, was treated with high dose of oral prednisolone in combination with rituximab (1000 mg given once on day 1 and repeated on day 15) according to the rheumatology dosing regimen. Because the patient developed erythema multiforme, he was switched to dexamethasone pulse therapy followed by oral dexamethasone, 4 mg per day, as described by Kardaun and Jonkman.<sup>15</sup> On day 57 after the first rituximab dosage he developed PCP. The patient subsequently required mechanical ventilation and treatment with trimethoprim-sulfamethoxazole and to date is making a full recovery.

Based on the sample size of 801 patients, an estimated 28 patients (3.5%) would need to develop PCP to justify prophylaxis. Comparison of the predicted incidence cut-off (3.5%) to the actual incidence (0.1%) showed  $\chi^2_1$  ( $n = 801$ ) = 27.0 ( $P < .001$ ). To determine whether our sample was significantly lower than that previously reported in the literature for all dermatologic patients, the actual incidence (0.1%) was compared with the previously reported incidence (1.3%) demonstrating  $\chi^2_1$  ( $n = 801$ ) = 8.2 ( $P = .004$ ).

A subgroup analysis of the incidence of PCP in patients receiving rituximab demonstrated an incidence of 1 of 140 (0.7%), which compared with the predicted incidence cut-off (3.5%) showed  $\chi^2_1$  ( $n = 140$ ) = 3.3 ( $P = .07$ ).

**Table 2.** Demographics of 801 Patients With Autoimmune Blistering Disease Included in the Present Study

Total sample size	No. (%)
Follow-up, mean (SD), y	2.94 (3.25)
Age, mean (SD), y	66.47 (17.62)
Female sex	465 (58.0)
Disease subtype	
Pemphigus foliaceus	51 (6.4)
Pemphigus vulgaris	360 (44.9)
Bullous pemphigoid	322 (40.2)
Epidermolysis bullosa acquisita	13 (1.6)
Mucous membrane pemphigoid	54 (6.7)
Anti-p200 pemphigoid	1 (0.1)
Medications reviewed	
Oral corticosteroid	651 (81.2)
Azathioprine	270 (33.7)
Mycophenolate	113 (14.1)
Methotrexate	66 (8.2)
Cyclosporine	5 (0.6)
Rituximab	140 (17.5)
Intravenous immunoglobulin	34 (4.2)
Oral tetracyclines	120 (15.0)
Cyclophosphamide	28 (3.5)
Comorbidities <sup>a</sup>	
Hypertension	244 (39.4)
Diabetes mellitus	175 (22.9)
Osteoporosis	49 (7.9)
Psoriasis	10 (1.6)
Malignant neoplasm	59 (9.7)
Autoimmune disease	45 (7.3)
Pneumocystis pneumonia incidence	
3 months from initial presentation	1 (0.1)

<sup>a</sup> Percentage based on medical records in which comorbidities were available.

Because patients with pemphigus often require more significant immunosuppression than patients with pemphigoid, we performed a subgroup analysis of the 1 of 411 patients with PCP and pemphigus (0.2%), which compared with the predicted incidence cut-off (3.5%) showed  $\chi^2_1$  (n = 411) = 9.7 (P = .001). An additional subgroup analysis excluding patients receiving topical steroids, oral tetracyclines, and intravenous immunoglobulin demonstrated an incidence of 1 of 686 (0.14%), which was also significantly smaller than the proposed 3.5% incidence cut-off for prophylaxis use  $\chi^2_1$  (n = 686) = 21.6 (P = .001).

## Discussion

Patients with AIBD might represent a unique group of iatrogenically immunosuppressed patients. While these patients typically require prolonged use of often multiple immunosuppressive therapies, they may have a lower risk of PCP compared with other dermatologic conditions requiring iatrogenic immunosuppression. Because determining the utility of PCP prophylaxis requires a knowledge of the incidence of PCP in patients not receiving routine prophylaxis, it is essential to characterize this incidence by disease type.

Our study of the largest cohort of patients with AIBD highlights the relatively low risk of PCP, with the incidence falling significantly below that of the 3.5% recommended for initiating PCP prophylaxis.<sup>2</sup> In addition, our study was sufficiently powered to demonstrate that the incidence of PCP in all dermatologic patients (1.3%) significantly overestimated the incidence in patients with only immunobullous diseases. Thus, the use of routine prophylaxis against PCP in patients with AIBD could not be supported by our data.

Because only 1 patient developed PCP, we could not define clear risk factors from our study. This patient developed PCP while receiving both high-dose oral glucocorticoids and after receiving rituximab. He did not have any underlying pulmonary abnormalities, lymphopenia, or neutropenia. In a study of Chinese patients with AIBD, those who developed PCP had absolute lymphocyte counts ranging from 330 to 1200/ $\mu$ L.<sup>10</sup> This might indicate that routine laboratory monitoring could identify patients with lymphopenia, prompting either a switch in immunosuppressive therapy, or temporary PCP prophylaxis. Likewise, in a review of all reported cases of PCP developing in dermatology patients, Gonzalez Santiago et al<sup>12</sup> described 7 patients who developed PCP, 6 of whom had either lymphopenia, malignant neoplasm, or pulmonary fibrosis and 1 without a

description of comorbidities. All of these are known risk factors for PCP, particularly lymphopenia.

### **Limitations**

Our study has several limitations owing to its retrospective nature. Identification of diagnoses was based on medical records and database review. Multiple criteria to confirm the diagnosis of PCP were chosen to increase the sensitivity for identifying this diagnosis. The medical records of patients who received treatment prior to their referral to tertiary AIBD centers were reviewed for history of pneumonias to avoid underestimation of PCP cases. Cases of pneumonia and atypical pneumonia were all analyzed to ensure that patients did not receive treatment for PCP but rather received antibiotics, such as macrolides or cephalosporins. Still, given that the study captures patients from an initial visit to a tertiary care center with a minimum of 3 months of follow-up, there is a potential for underestimation. This may, however, be balanced by the more severe cases treated in a tertiary care center. Determining duration, treatment courses, or extent of concomitant use of different medication doses could not be performed to further stratify the level of immunosuppression in our population because information from previous medical record systems was summarized in binary form when integrated into newer electronic medical records or databases. Thus, a patient who received simultaneous prednisone and mycophenolate could not be routinely differentiated from a patient receiving prednisone and then later requiring mycophenolate. Further prospective evaluation accounting for the degree of immunosuppression (eg, treatment courses, concomitant therapies) would be beneficial for comparison with other immunosuppressed states. This particularly is true for the use of topical corticosteroids because a patient who received daily whole-body clobetasol would not be considered to be on systemic immunosuppression, despite the significant level of systemic immunosuppression that occurs with this protocol.<sup>16</sup> To counter this, all patients with immunobullous disease, whether receiving systemic immunosuppression, were included in the study. Still, a subgroup analysis was performed of patients receiving only systemic immunosuppressive therapy, and our findings of low PCP incidence were not changed even in this high-risk cohort. In addition, the exclusion of patients prescribed dapsone decreased the number of patients assessed. Our study was underpowered to assess the incidence of PCP in patients with AIBDs receiving rituximab. Thus, while the PCP incidence in this group

was not significant below the proposed threshold of 3.5%, a larger study would be required to verify this. Finally, our study was performed at tertiary and quaternary care centers, where more aggressive therapies may be used than in community practice. The inclusion of patients from 2 continents and 6 centers, however, improves the generalizability to the larger cohort of patients with AIBDs.

## Conclusions

The high mortality of PCP warrants significant discussion in regard to prophylaxis; however, the incidence of PCP in the disease population must surpass the risks of prophylactic therapy. We demonstrate in a large, multinational cohort of patients with AIBDs that the incidence of PCP does not pass muster. Thus, even in patients with immunobullous disorders receiving various systemic immunosuppressive therapies in the routine clinical setting, lack of prophylaxis was not associated with a sufficient incidence of PCP to warrant prophylaxis.

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